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Magnetic Nonequivalence in Higher Alkyl Groups

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University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a thesis written by Philip Anthony Reitano entitled "Magnetic Nonequivalence in Higher Alkyl Groups." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

N.S Bowman, Major Professor

We have read this thesis and recommend its acceptance:

George W. Kavalka, James Q. Chauser

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Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

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167

September 5, 1972

To the Graduate Council:

I am submitting herewith a thesis written by Philip Anthony Reitano entitled "Magnetic Nonequivalence in Higher Alkyl Groups." I recommend that it be accepted for eighteen quarter hours of credit in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry..

H. S. Sherman
Major Professor

We have read this thesis
and recommend its acceptance:

George W. Kavalka

James A. Chamberlain

Accepted for the Council:

Hilton A. Smith
Vice Chancellor for
Graduate Studies and Research

MAGNETIC NONEQUIVALENCE IN HIGHER ALKYL GROUPS

A Thesis

Presented to

the Graduate Council of

The University of Tennessee

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

---

by

Philip Anthony Reitano

December 1972

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ABSTRACT

The phenomenon of magnetic nonequivalence has been growing in recent years. Unequal populations of the various conformers in such molecules are normally accepted as the cause of nonequivalence, but nuclei which are stereochemically nonequivalent are not necessarily magnetically nonequivalent. This nonequivalence has been demonstrated for molecules of the type $ABDC^{*}CHR_1R_2$, where R = H, F, and Me. Although in principle the effect is quite general this has not been previously observed in "freely rotating" systems for groups larger than methyl. The role of steric factors, the size of the substituents and the distances between different parts of the molecules, have been discussed. In the present investigation these observations have been extended to demonstrate magnetic nonequivalence in higher groups including ethyl, isopropyl, propyl, isobutyl and benzyl by conversion of the appropriate alcohols to their mandelate esters.

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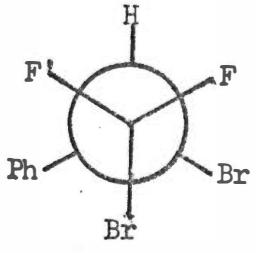
INTRODUCTION

A. General

In 1957 Drysdale and Phillips[1] noted that the fluorine spectrum of $CF_2BrCHBrPh$ instead of appearing as the anticipated simple doublet showed the multiplicity of eight lines expected from the AB region of an ABX spectrum. These authors pointed out that in each of the three most probable conformations the fluorines, with different enviornment, are magnetically nonequivalent, and thus have different chemical shifts.



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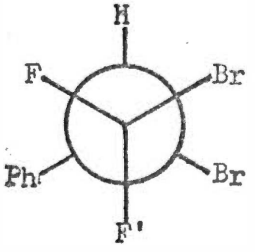

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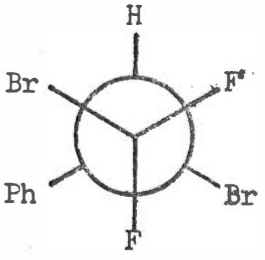


III

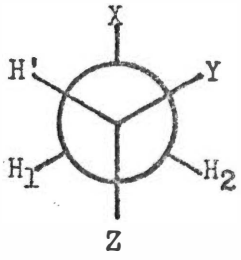
If, therefore, the conformers are unequally populated, the weighted average of the chemical shifts for the two fluorines are not equal, and thus display an AB spectral region rather than the A_2 normally expected. The rotationally averaged proton shifts (ν) of two geminal fluorines, F and F^1, are given by

$$\nu_{F^i} = \sum_n X_n \nu_n^{F^i} \qquad \nu_F = \sum_n X_n \nu_n^F \tag{1}$$

where X_n is the mole fraction of rotamer n and ν_n^i is the resonance frequency, or chemical shift, of the i^{th} nucleus in rotamer n.

Pople and Gutowsky[2,3] have pointed out that asymmetry effects can give rise to nonequivalent nuclei even though conformational populations are equal, but population differences do not necessarily lead to nonequivalence unless the molecular asymmetry is great enough. In the absence of restricted rotation, geminal groups will be magnetically nonequivalent if the molecule can assume more than one conformation, and if the magnetic enviornments of the groups in question are different in these conformations. Unequal populations of the various conformers in such molecules is normally accepted as the cause of nonequivalence, but nuclei which are stereochemically nonequivalent are not necessarily magnetically nonequivalent.

Pople[4] considered the possible splitting patterns that could arise in various substituted ethanes. These results can be generalized and expanded by considering a trisubstituted ethane CH_2X-CHYZ for which the three forms are physically distinct and may have different populations. In each individual isomer,



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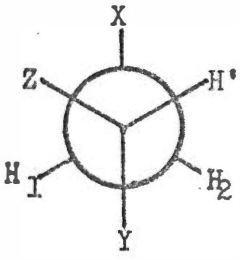

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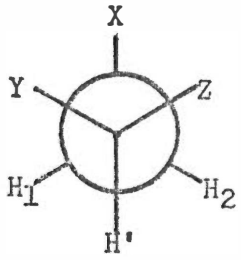
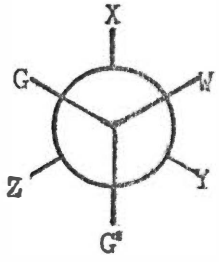


VI

there are three nonequivalent protons so, for slow rotation, the total spectrum will be a superposition of three types of ABX. But even if rotation is rapid, the average enviornment of H_1 will differ from that of H_2 so that once again the spectrum will appear to be that of three nonequivalent nuclei giving rise to a single ABX spectrum.

The origin of nonequivalence has usually been ascribed to differences in conformer population. However, Waugh and Cotton[5] have explicitly mentioned that a symmetry argument alone completely independent of any facts of conformational isomerism, could equally well account for such nonequivalence, although some workers have not seemed to take cognizance of this alternative.

It has been known that in systems of the type $CXYZCG_2W$, where W, X, Y, Z are atoms or groups of atoms, and G is magnetically active, the G nuclei sometimes display magnetic nonequivalence.



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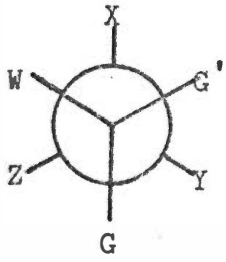

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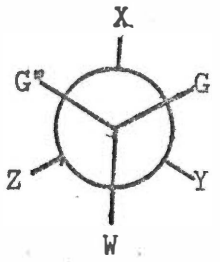


IX

This phenomemon has been observed for the methylene hydrogens in the ethyl group of ethers, sulfites, sulfoxides, carboxylic esters, methylene hydrogens in variously tetrasubstituted ethanes and for the methyl groups of various systems containing an isopropyl skeleton to mention but a few.[6]

B. Origin of Nonequivalence

The term "magnetic nonequivalence" leads to semantic confusion which needs clarification. In general, the only two criteria which can be conveniently applied to differentiate magnetically between nuclei are the chemical shift difference between the nuclei and the spin coupling constant of these nuclei with some third one. It would therefore be preferable to classify nuclei as being either magnetically nonequivalent in the chemical shift or in the spin coupling sense. As shall become clear, nuclei which are nonequivalent by one criterion may be equivalent

according to the other. It must be emphasized that in suitable $CXYZCG_2W$ systems the G nuclei are always stereochemically nonequivalent but not necessarily magnetically nonequivalent.

As it appears, the subject of magnetic nonequivalence has a number of distinct, but not wholly independent aspects: (A) What are the broad characteristics of systems which have nonequivalent nuclei? (B) What sort of behavior is exhibited by nonequivalent nuclei? (C) What are the origins of nonequivalence? (D) What quantitative relations can be developed linking information gathered from systems possessing nonequivalent groups and conformational rotational isomerism?

It has been shown[7] that for certain types of substituted ethanes, any single measurement of the proton spectrum does not necessarily distinguish between slow and rapid rotation. The variation of the spectrum with temperature, however, may provide significant additional evidence. Thus, if the rotation is rapid, the various effective chemical shifts and coupling constants will be averages of the values for the possible rotamers. Thus the chemical shift parameters δ for a pair of nuclei will have an effective value.

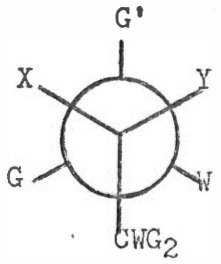
$$\delta_{obs} = \delta_1 N_1 + \delta_2 N_2 + \delta_3 N_3 \qquad (2)$$

where δ_1, δ_2, δ_3 are the chemical shift values corresponding to the separate rotamers and N_1, N_2, N_3 are weighting factors. If the three rotamers are not equally populated, these weighting factors will be temperature dependent.

The problem of possible importance of small contributions to magnetic nonequivalent can arise from an "intrinsic" asymmetry, independent of rotational conformer populations. The term intrinsic signifies that the observed nonequivalence is not dependent on temperature. However, it should be emphasized that in discussing the relative importance of conformational preferences and intrinsic asymmetry, the question at issue is not whether the former or the latter is alone responsible for magnetic nonequivalence, but rather how much of any of an observed nonequivalence should be ascribed to intrinsic asymmetry. There seems little doubt that conformational preference with respect to the asymmetric center must in general be responsible for the major contributions to the magnetic nonequivalence.[8]

This nonequivalence has been previously demonstrated for molecules of the type $CXYZCG_2W$ where G=H, F and Me.[9] Although in principle the effect is quite general this has not been observed in "freely rotating" systems for groups larger then methyl. The purpose of this research is to demonstrate the generality of magnetic nonequivalence by extenting these observations to higher groups including ethyl, propyl, isopropyl, sec. butyl and benzyl.

In the examples given so far of molecules of the type $CXYZCG_2W$, there is a center of asymmetry. This is not a necessary requisite, however, since molecules of the type $CWG_2CXYCWG_2$ which contain no asymmetric center may also display magnetically non-equivalent G groups as is shown in structures X, XI, and XII.



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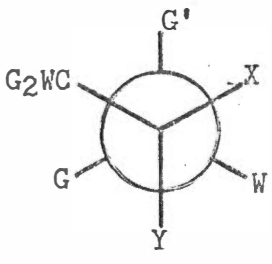

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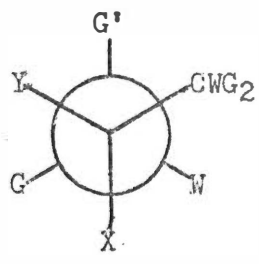


XII

Thus in the molecules included in this study which comprise the mandelic acid esters of alchols of the type RCHOHR, not only may the two R groups themselves be magnetically nonequivalent, but also geminal protons or methyl groups within a given R group.

CHAPTER II

EXPERIMENTAL

A. Synthesis

1. Preparation of 2,6-Dimethyl-4-Heptyl Mandelate

In a 200 ml bolt-head flask equipped with a Dean-Stark trap and a reflux condenser were mixed 6.1g (0.04 mole) of mandelic acid, 17.3g (0.12 mole) of 2,6-dimethyl-4-heptanol, 75 ml of benzene and 0.3 ml of concentrated sulfuric acid. After six hours of reflux, the unreacted acid was neutralized by the addition of a dilute solution of sodium carbonate. The benzene and excess alcohol were then distilled from the reaction mixture under aspirator vacuum. The product was collected at 125°/2.5mm giving 76% yield (8 gms). The ester was then recrystallized from pentane M. P. 37-38°.

Anal. calculated for $C_{16}H_{26}O_3$: C, 73.48 ; H, 9.41.
Found: C, 72.83; H, 9.28.

2. Preparation of 2,4-Dimethyl-3-Pentyl Mandelate

In a 200 ml bolt-head flask equipped with a Dean-Stark trap and a reflux condenser were mixed 6.1g (0.04 mole) of mandelic acid, 13.8g (0.12 mole) of 2,4-dimethyl-3-pentanol, 75 ml of benzene and 0.3 ml of concentrated sulfuric acid. After six hours of reflux, the unreacted acid was neutralized by the addition of a dilute solution of sodium carbonate. The benzene

and excess alcohol were then distilled from the reaction mixture under aspirator vacuum. The product was collected at 130°/2.0mm in 63% yield (6gm). The ester was then recrystallized from pentane. M. P. 52-53°.

Anal. calculated for $C_{14}H_{22}O_3$: C, 71.96; H, 8.85. Found: C, 71.92; H, 8.76.

3. Preparation of 4-Heptyl Mandelate

In a 200 ml bolt-head flask equipped with a Dean-Stark trap and a reflux condenser were mixed 6.1g (0.04 mole) of mandelic acid, 13.8g (0.12 mole) of 4-heptanol, 75 ml of benzene and 0.3 ml of concentrated sulfuric acid. After 6 hours of reflux, the unreacted acid was removed by the addition of a dilute solution of sodium carbonate. The benzene and excess alcohol were then distilled from the reaction mixture under aspirator vacuum. The product was collected at 125°/1.5mm in 85% yield (7 gms). The ester was recrystallized in ligroine. M. P. 43-44°.

Anal. calculated for $C_{14}H_{22}O_3$: C, 71.96; H, 8.85. Found: C, 71.89; H,8.61.

4. Attempted Preparation of Diphenyl Methyl Mandelate

In a 200 ml bolt-head flask equipped with a Dean-Stark trap and a reflux condenser were mixed 6.1 gm (0.04 mole) of mandelic acid, 22.08 gms of diphenyl methanol, 75 ml of benzene and 0.3 ml of concentrated sulfuric acid. After eight hours of reflux the unreacted acid was removed by addition of a dilute

solution of sodium carbonate. The benzene and excess alcohol were then distilled from the reaction mixture under aspirator vacuum. The product was collected at $135^{o}/2.0$mm. The ester was then recrystallized in ligroine to give a melting point of $102\text{-}104^{o}$. The NMR of the product gave a spectrum not consistant with the proposed spectrum, and did not show a hydroxyl change in CCl_4, which indicates the nonexistance of an hydroxyl group. The IR of the product was then taken and no hydroxyl band exists. On the bases of these data as well as the analysis of the compound, it was concluded that the desired esterification was not obtained. Repeated attempts yielded similar results, and the synthesis was abandoned in favor of the esterification of 1,3-diphenyl-2-propanol.

5. Preparation of 1,3-Diphenyl-2-Propyl Mandelate

In a 200 ml bolt-head flask equipped with a Dean-Stark trap and a reflux condenser were mixed 6.1gm (0.04 mole) of mandelic acid, 21.2gms (0.10 mole) of 1,3-diphenyl-2-propanol, 75 ml of benzene and 0.3 ml of concentrated sulfuric acid. After 30 hours of refluxing, the unreacted acid was neutralized by the addition of a dilute solution of sodium carbonate. The benzene and excess alcohol were then distilled from the reaction mixture under aspirator vacuum.

A chromatography column was then set up using alumina and eluting with benzene. Impurities were removed by twelve 100 ml cuts leaving the product on the column. The ester was then eluted with a 1:1 acetone/ether mixture which yielded a

pale straw color liquid after evaporation of the solvent. The crude ester was recrystallized from ligroine. M. P. 62° .

Anal. calculated for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.90; H, 6.19.

6. Preparation of 3-Pentyl Mandelate

In a 200 ml bolt-head flask equipped with a Dean-Stark trap and a reflux condenser were mixed 6.1g (0.04 mole) of mandelic acid, 10.5g (0.12 mole) of 3-pentanol, 75 ml of benzene and 0.3 ml of concentrated sulfuric acid. After six hours of reflux, the unreacted acid was neutralized by the addition of a dilute solution of sodium carbonate. The benzene and excess alcohol were then distilled from the reaction mixture under aspirator vacuum. The product was collected at 125°/2.0mm in 85% yield (7.5 gms). The ester was recrystallized from ligroine. M. P. 38° .

Anal. calculated for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.88, H, 8.18.

B. Instruments Used to Obtain Analytical Data

1. Nuclear Magnetic Resonance

A Varian A-60 and a Varian HA-100 were used, and all values of Hz in the body of this thesis are refered to the 100MHz.

2. Melting Points

All melting points were taken using a Mel-temp electrical heating apparatus and are noncorrected.

3. Infrared

Limited data were obtained using the Perkin Elmer Infracord Model 137.

All studies and odservations were done at room temperature.

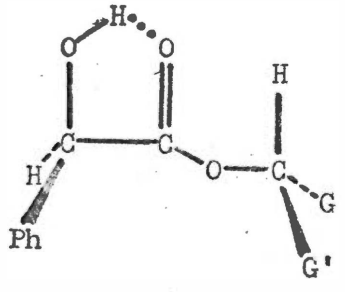
CHAPTER III

RESULTS

The spectra of a series of mandelic acid esters were obtained at 10 mole per cent in CCl_4. Mandelic acid contains an asymmetric center. Even though this asymmetric center is not bonded directly to the site of nonequivalence, definite nonequivalence in remote parts of the molecules has been observed.

In these esters the change in chemical shift at the hydroxyl methine position on esterification is considerably larger than that normally observed. The shift most commonly accepted on esterification for the methine proton of secondary alcohols is approximately 1.00-1.15p.p.m.

There is ample evidence that esters of alpha-hydroxy acids are intramolecularly hydrogen bonded. This apparently impresses a highly preferred arrangement of the assymmetric center relative to the carbonyl group as indicated in the following structure:



V

A. 3-Pentyl Mandelate

The spectrum of the alcohol 3-pentanol consists of a triplet for the two methyl groups centered at 90 Hz and a multiplet for the methylenes centered at 143 HZ. The methine resonance is a quintet at 335.5 Hz. This is characteristic of an $(A_3B_2)_2X$ system. Table I lists some 100 MHz data.

The mandelate ester of this alcohol displays definite nonequivalence with a doublet of triplets representing the two methyl groups. The upfield methyl is located at 47 Hz and the downfield one at 80 Hz. This represents an upfield shift of 43 Hz and 10 Hz relative to the alcohol. The methylene region shows two sets of overlapping pseudo-first order quintets, with the downfield section of the higher field methylene overlapping the upfield section of the lower field methylene as shown in Figure 1. Relative to 3-pentanol itself, one geminal set of methylene resonances of the ester has been shifted upfield to 132 Hz and 137 Hz, while that of the other methylene has been shifted downfield to 150 Hz and 152 Hz. This represents an upfield shift of one pair of methylenes of 11 Hz and 6 Hz and a downfield shift of the other methylenes of 7 Hz and 9 Hz. Furthermore, the high field methylene resonances are associated with the high field methyl group. The methine region has shifted downfield 136.2 Hz to 471.7 Hz.

The most reasonable interpretation of these data is that one ethyl group is shielded as a consequence of lying over the phenyl ring.

TABLE I

SPECTRAL PARAMETERS (IN HZ) FOR 3-PENTANOL, AND 3-PENTYL MANDELATE AT 100 MHZ

	3-Pentanol	3-Pentyl Mandelate Low-Field Ethyl Group	3-Pentyl Mandelate High-Field Ethyl Group
ν_X	335.5	471.7	
ν_B	141.3	150.3	131,5
ν_A	145.6	152.4	137.1
ν_C	91.1	83.7	47.6
J_{BX}	6.98	6.13	7.18
J_{AX}	5.22	6.27	5.14
J_{BC}	7.51	7.48	7.56
J_{AC}	7.38	7.48	7.28
J_{AB}	-18.88	-13.64	-13.42

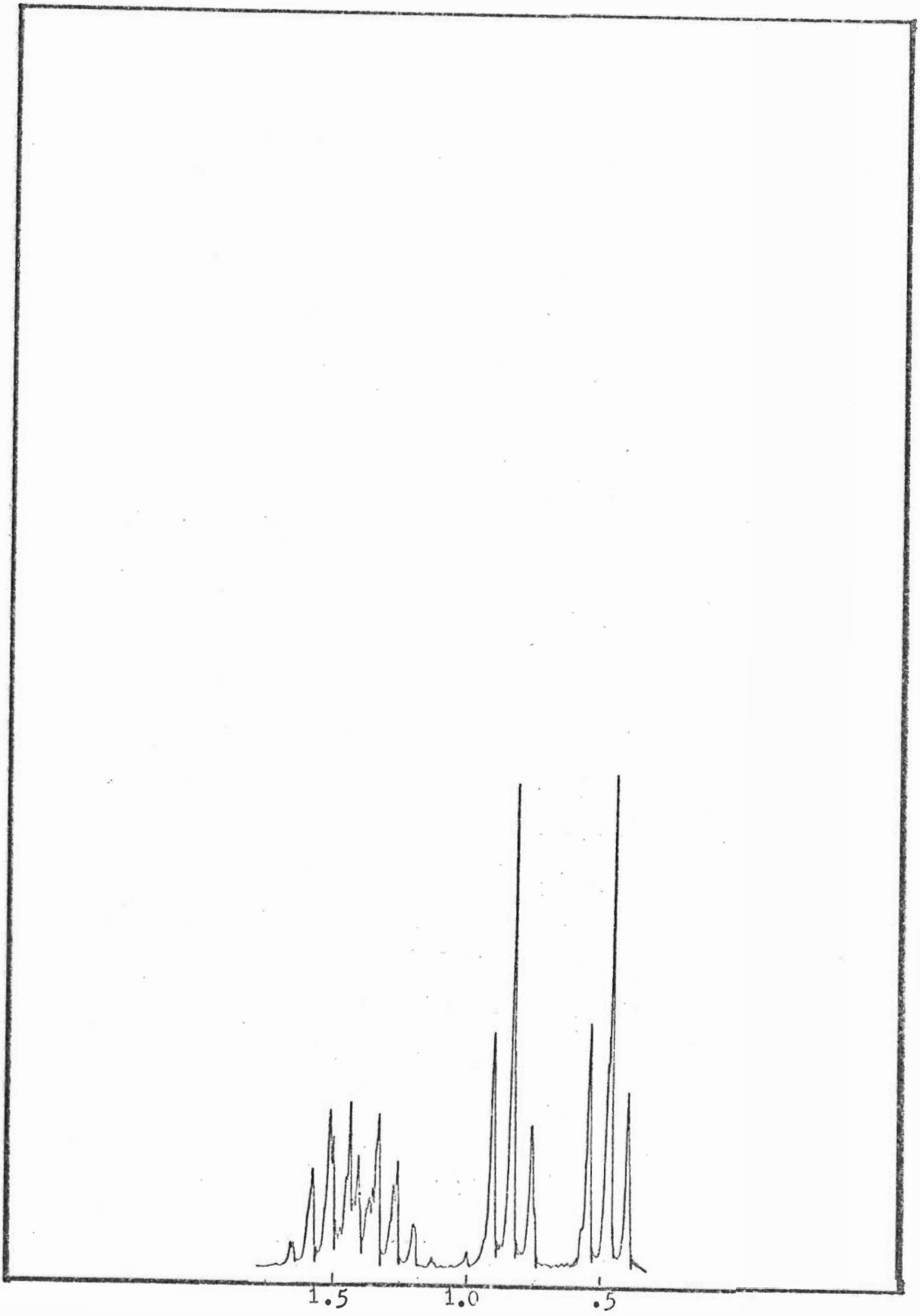
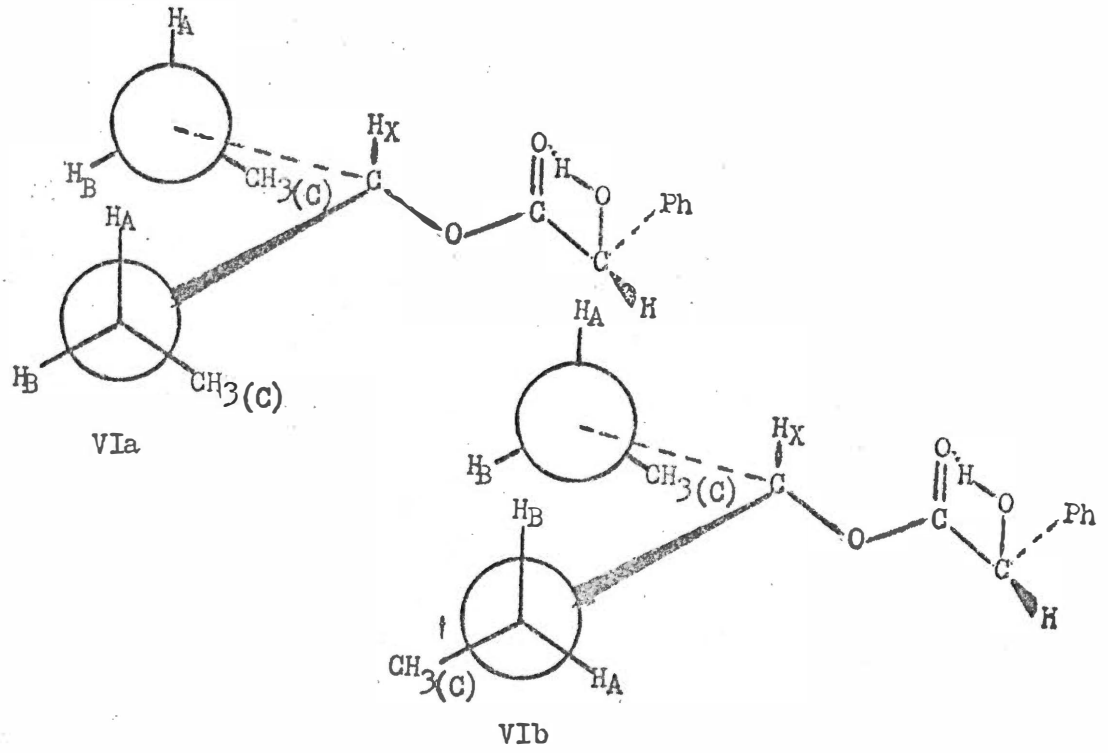


Figure 1. Methyl and methylene region of 3-pentyl mandelate @ 100MHz.

Structures VIa and VIb show two possible conformations of 3-pentyl mandelate. This ester has been explicitly analyzed by computer as an $ABCDE_3F_3X$ system by a NMRIT-NMREM program,[10] and Table I lists the data obtained.



B. 2,4-Dimethyl-3-Pentyl Mandelate

The spectrum of the alcohol consists of a doublet for the methyl groups at 80.5 Hz a multiplet centered at 168.5 Hz for the isopropyl methines, and a triplet at 292 Hz for the hydroxyl methine. This is characteristic of a $(A_6B)_2X$ system.

The mandelate ester of this alcohol shows three different methyl groups: one at 52 Hz, an other at 47 Hz and the two superimposed methyl groups centered at approximately 86 Hz. This represents an upfield shift of one methyl of 33.5 Hz, another methyl of 28.5 Hz

and a downfield shift of a pair of methyls of approximately 6 Hz. The hydroxyl methine appears as a doublet of doublets at 456.5 Hz from which is concluded that:

1.) The coupling between the two isopropyl methines and hydroxyl methine is unequal.

2.) The isopropyl methines have unequal chemical shifts.

If either of the above were untrue, the hydroxyl methine would appear as a 1:2:1 triplet.

The isopropyl methines consists of complex splitting patterns lying between 204 Hz and 146 Hz. If the three methine protons are considered as an ABX system the X region which consist of the hydroxyl methine should contain four lines. In view of nonequivalence established in the mandelate of 3-pentanol, any effort to make assignment of the isopropyl methine region of the spectrum is not warrented, because twenty-eight lines would be expected in this region. Due to low intensity and superimposition of some lines rigorous analysis is impossible.

Spectra of this type are usually interpreted by considering the coupling constants J_{AX} and J_{BX} as perturbations of energy levels in absence of coupling.[11] Thus the quantities D_+ and D_- may be defined by the following relationships:

$$D_+ = \tfrac{1}{2}\left\{\left[(\nu_A - \nu_B) + \tfrac{1}{2}(J_{AX} - J_{BX})\right]^2 + J_{AB}^2\right\}^{\frac{1}{2}} \qquad (3)$$

$$D_- = \tfrac{1}{2}\left\{\left[(\nu_A - \nu_B) - \tfrac{1}{2}(J_{AX} - J_{BX})\right]^2 + J_{AB}^2\right\}^{\frac{1}{2}} \qquad (4)$$

Values of D_+ and D_- can be obtained in principle by subtraction of

appropriate band frequencies; then using the above equations J_{AX} and J_{BX} may be calculated. Using the numbering convention of Pople,[12] the frequencies of the following lines are used in determining the two quantities D_+ and D_-.

$$2D_+ = 6\text{-}2 = 8\text{-}4 \quad (5)$$

$$2D_- = 5\text{-}1 = 7\text{-}2 \quad (6)$$

But due to the complexity of the spectrum of 2,4-dimethyl-3-pentyl mandelate, the necessary lines involed cannot be assigned with confidence.

Comparing the chemical shift data of 2,4-dimethyl-3-pentyl mandelate with the rigorously analyzed 3-pentyl mandelate, it is logical to conclude that:

1.) By comparison with the nonequivalent methylenes in the 3-pentyl mandelate, the isopropyl methine protons of 2,4-dimethyl-3-pentyl mandelate must exhibit a change in chemical shift of 14-19 Hz with respect to the alcohol.

2.) Nonequivalent coupling of the four methylene protons of the 3-pentyl mandelate with the hydroxyl methine on the pentyl chain would support a similar coupling with the adjacent two protons in the 2,4-dimethyl-3-pentyl mandelate.

The conformations which most suitable agree with these data are shown in structures VIIa and VIIb and the data in Table II along with

TABLE II

SPECTRAL PARAMETERS (IN HZ) FOR 2,4-DIMETHYL-3-PENTANOL, AND 2,4-DIMETHYL-3-PENTYL MANDELATE AT 100 MHZ

	2,4-Dimethyl-3-Pentanol	2,4-Dimethyl-3-Pentyl Mandelate	
		Low-Field Isopropyl Group	High-Field Isopropyl Group
ν_X	292	456	
ν_B	80.5	86	52, 47
ν_A	168.5	ASSIGNMENT NOT WARRENTED	
J_{AX}	6.5	6.7	6.7
J_{AB}	6.5	6.7	6.7

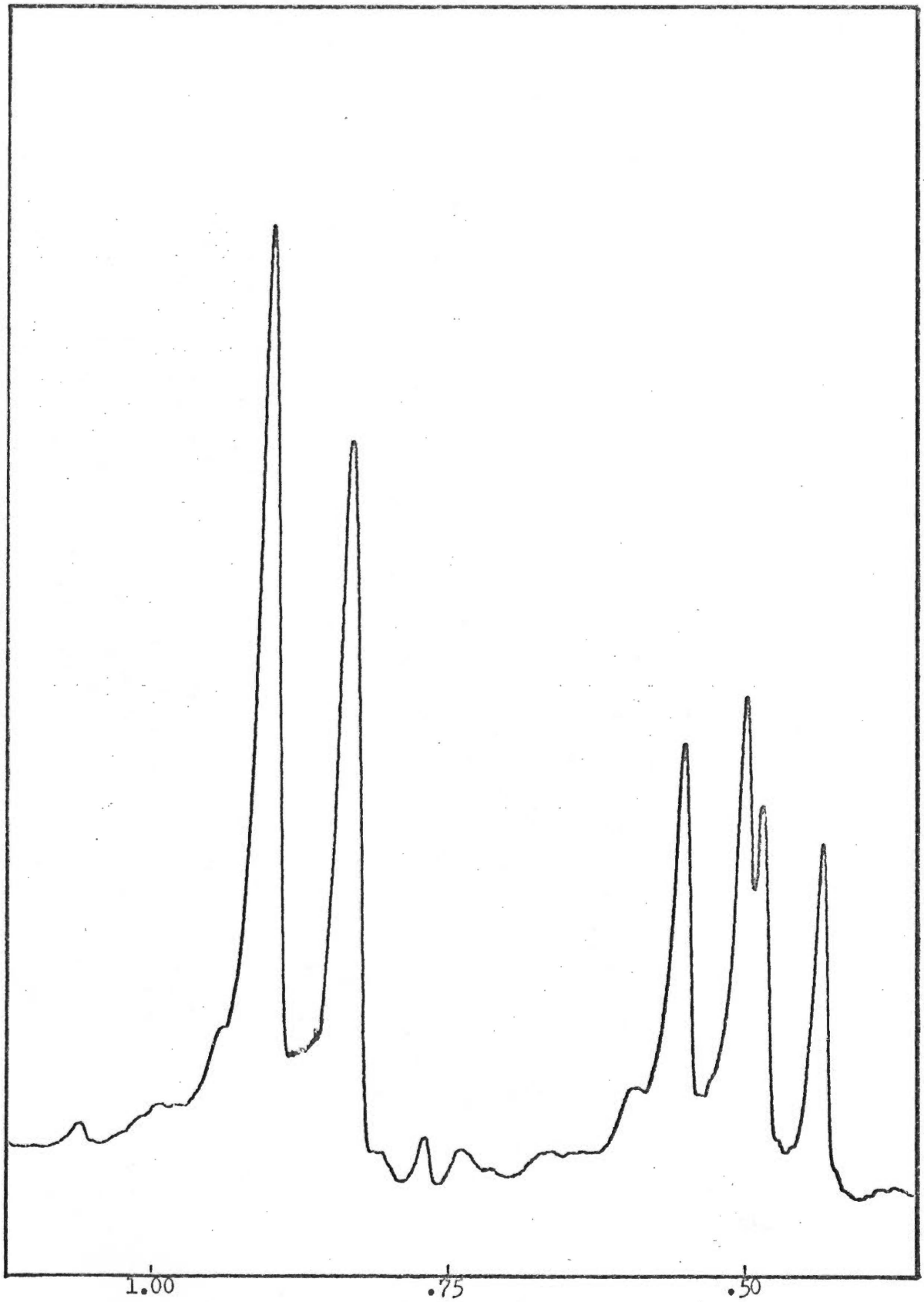


Figure 2. Methyl region of 2,4-dimethyl-3-pentyl mandelate @ 100MHz.

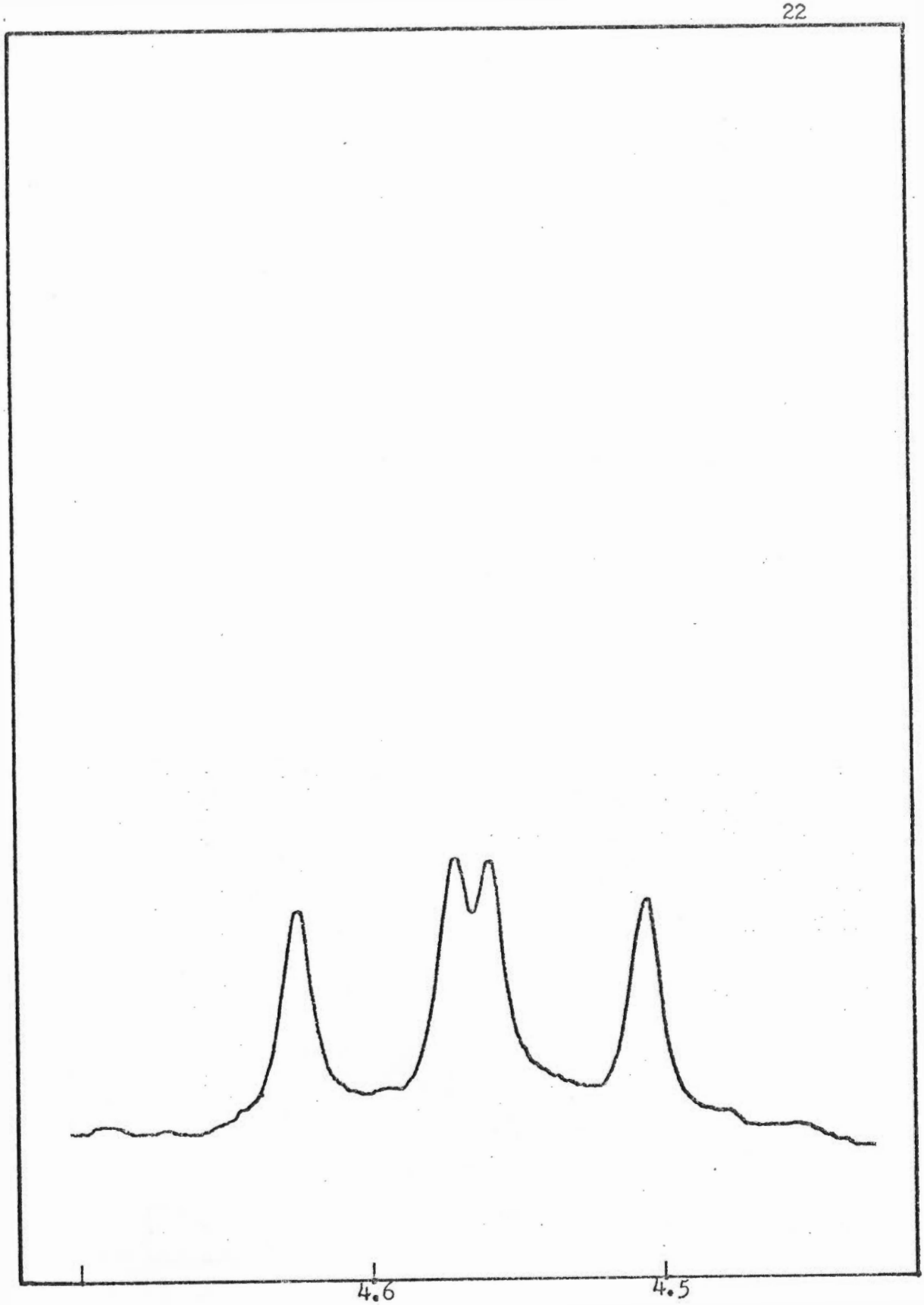
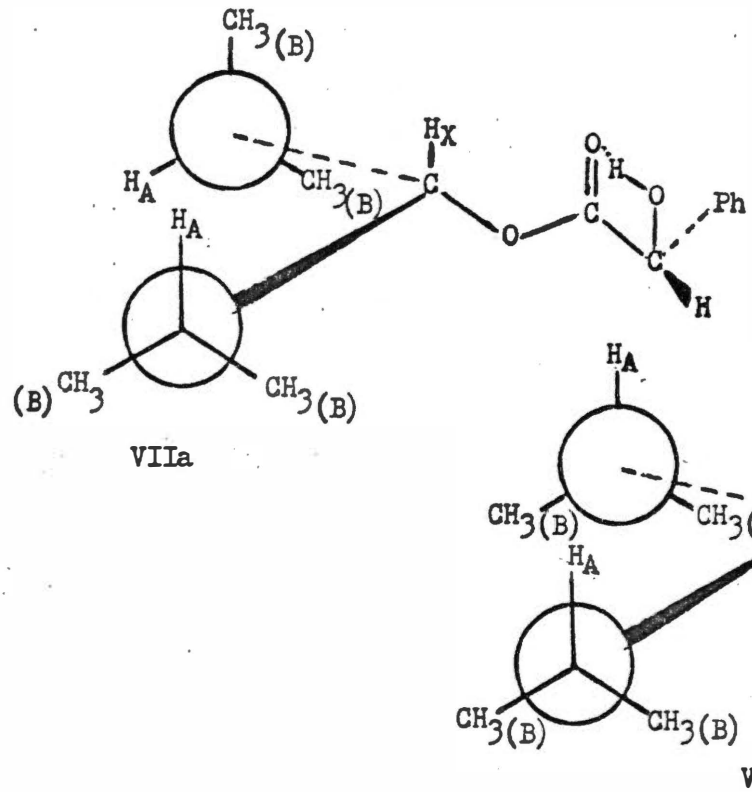
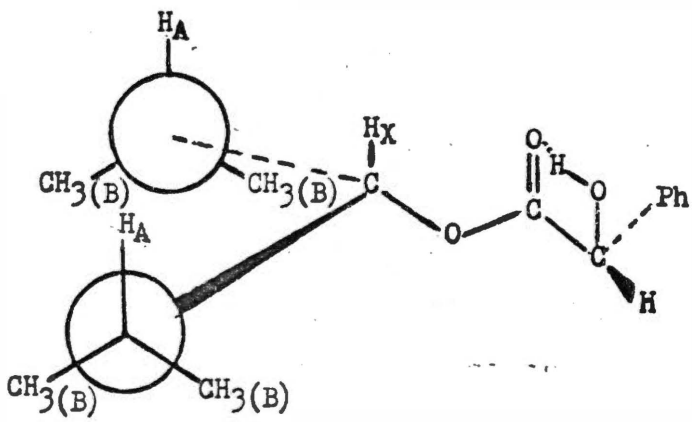


Figure 3. Methine region of 2,4-dimethyl-3-pentyl mandelate @ 100MHz.

Figures 2 and 3 show that the high field isopropyl group is located over the shielding cone of the phenyl, and the remaining isopropyl group located at either of the two positions shown by the structures.



VIIa



VIIb

C. 4-Heptyl Mandelate

The spectrum of the alcohol 4-heptanol consists of a triplet for the two methyl groups at 93.5 Hz and a multiplet centered between 137 Hz and 142 Hz for the four pairs of methylenes. The methine is a quintet centered at 352 Hz. This is characteristic of an $(A_3B_2C_2)_2X$ system.

The mandelate ester of this alcohol displays two different methyl groups; the upfield one at 65 Hz and the downfield methyl

group at 91 Hz, both with coupling constants of 6 Hz. This represents an upfield shift of one methyl of 28 Hz and an upfield shift of 2.5 Hz of the other methyl relative to the alcohol.

There are three different methylene groups represented by this ester spectrum. Two methylenes centered at approximately 89 Hz and approximately 135 Hz; the two methylenes remaining do not experience significant change in chemical shift with respect to 4-heptanol, and appear at 137 Hz and 142 Hz. The two upfield methylene groups have experienced changes in chemical shifts of approximately 48 Hz and 7 Hz. The methylene with the greater upfield shift has been buried under the downfield methyl group. Besides spectral appearance, this can be supported by integration which shows five protons at this position, three for the downfield methyl and two for the upfield methylene.

The methine appears as a quintet at 488 Hz with a coupling constant of 6 Hz. In as much as the expected first order splitting of the methine would be a quintet, this signifies that either:

1.) The coupling between the methine and the methylene groups on either side is the same, or

2.) The sum of the coupling constants between the methine proton and pair of geminal methylenes is the same.

In assigning conformation that most suitably match these data, the upfield propyl half of the ester lies above the plane of the phenyl ring where it would experience the anisotropic shielding of the benzene nucleus. Table III and Figure 4 will show by analogy

TABLE III

SPECTRAL PARAMETERS (IN HZ) FOR 4-HEPTANOL, AND 4-HEPTYL MANDELATE AT 100 MHZ

	4-Heptanol	4-Heptyl Mandelate Low-Field Propyl Group	4-Heptyl Mandelate High-Field Propyl Group
ν_X	352	488	
ν_A	93.5	91	65
ν_B	~137	~135	89
ν_C	~142	~142	~137
J_{AB}	6.0	6.0	6.0
J_{BC}	6.0	ASSIGNMENT NOT WARRENTED	
J_{CX}	6.0	6.0	6.0

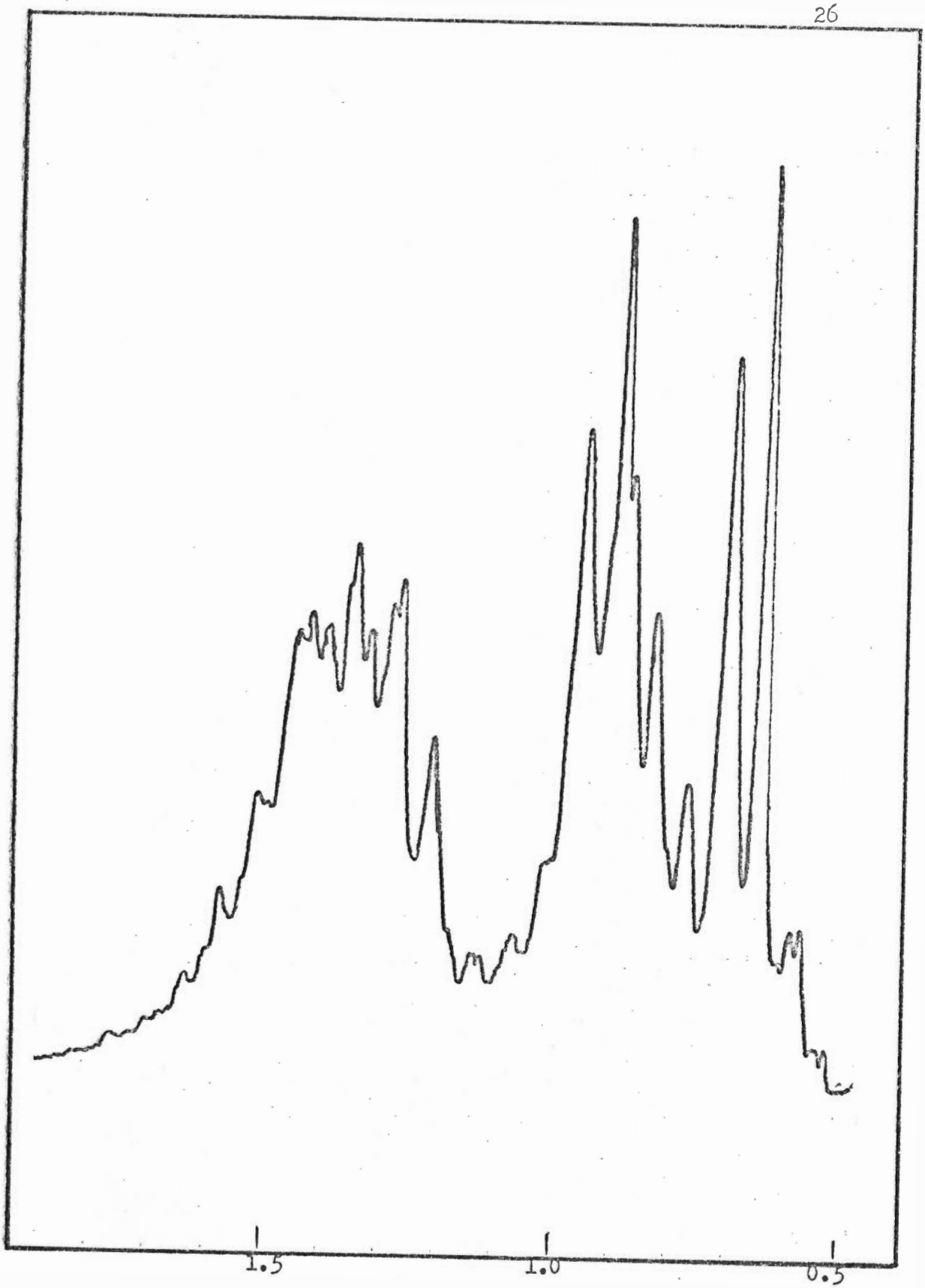
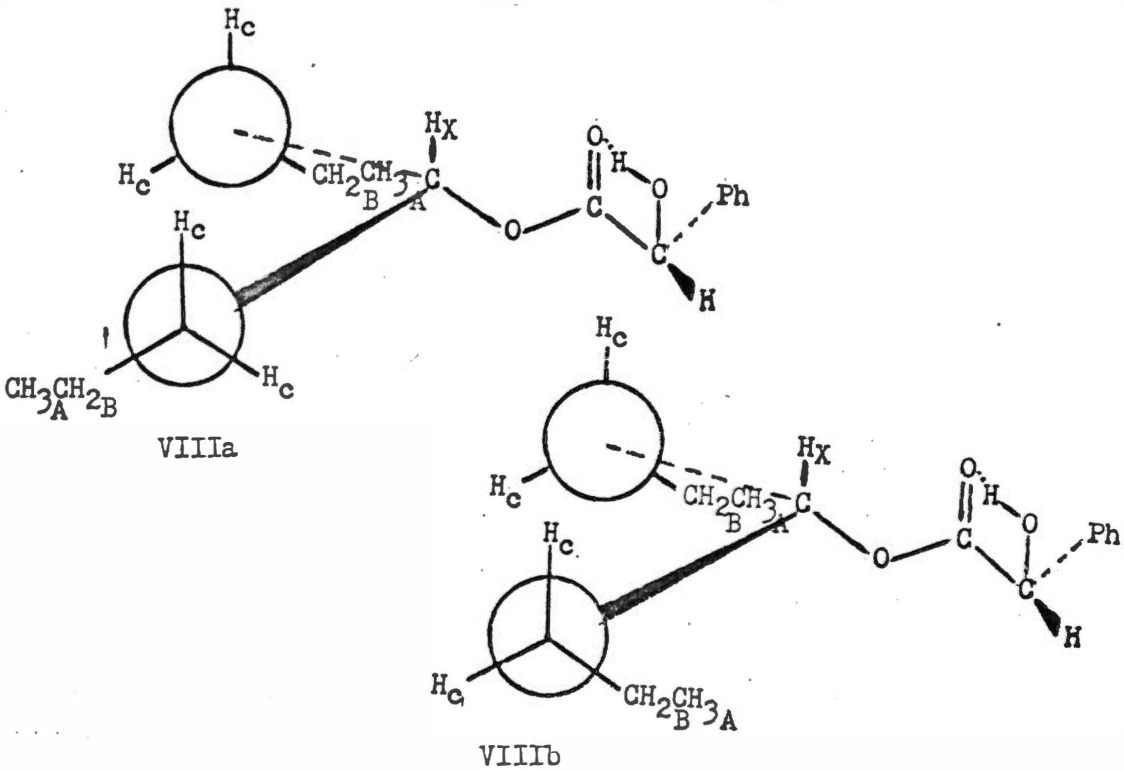


Figure 4. Methyl and methylene region of 4-heptyl mandelate @ 100MHz.

with the explicitly analyzed 3-pentyl ester, these conformations are shown in structures VIIIa and VIIIb.



VIIIa

VIIIb

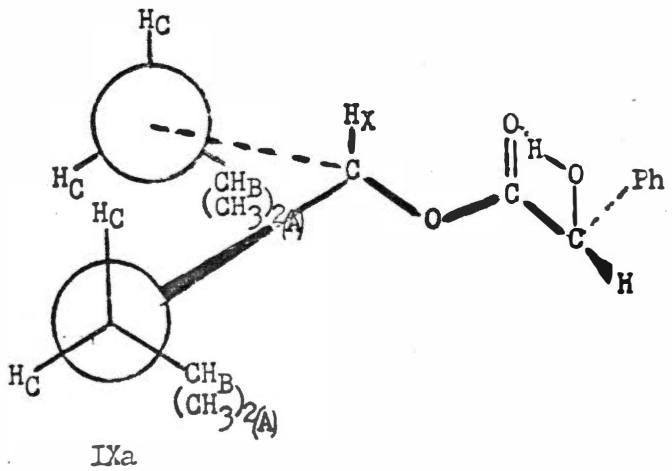
D. 2,6-Dimethyl-4-Heptyl Mandelate

The spectrum of the alcohol 2,6-dimethyl-4-heptanol consists of a doublet for the methyl protons at 93 Hz and a multiplet for the methylenes at 126 Hz. The isopropyl methine consists of a multiplet at 185 Hz. This is characteristic of an $(A_6BC_2)_2X$ system.

The mandelate ester of this alcohol displays definite non-equivalence, with two doublets of doublets representing the four methyl groups, an example of four magnetically different methyl

groups. The two upfield methyl groups at 75 Hz and 63 Hz represent an upfield shift of 18 Hz and 30 Hz relative to the alcohol. The two downfield methyl groups at 86.5 Hz and 89 Hz represent an upfield shift of 6.5 Hz and 4.0 Hz relative to the alcohol with coupling constants of 5.5 Hz. The methylene region is somewhat complex because the absorption of the high field methylene protons at approximately 94.7 Hz is buried under the low field methyl group, and the low field methylene group at approximately 121.7 Hz is partially overlapped with the high field isopropyl methine protons. The isopropyl methine protons as mentioned previously overlap the lowfield methylene protons.

The multiplet at 503.5 Hz represents the hydroxyl methine with a coupling constant of 4.5 Hz. This represents a downfield shift of 134 Hz relative to the alcohol. Any further interpretation of the spectrum is not warrented, but the most reasonable interpretation of these data is that one isobutyl group is shielded as a consequence of lying over the phenyl ring as shown in structures IXa and IXb and in Table IV and Figure 5.



IXa

TABLE IV

SPECTRAL PARAMETERS (IN HZ) FOR 2,6-DIMETHYL-4-HEPTANOL AND 2,6-DIMETHYL-4-HEPTYL MANDELATE AT 100 MHZ

	2,6-Dimethyl-4-Heptanol	2,6-Dimethyl-4-Heptyl Mandelate	
		Low-Field Isobutyl Group	High-Field Isobutyl Group
ν_X	352	503.5	
ν_A	93.5	89, 86.5	75, 63
ν_B	~ 137	~ 181.9	~ 147
ν_C	~ 142	~ 121.7	~ 94.7
J_{AB}	6.5	5.5	5.5
J_{BC}	6.5	ASSIGNMENT NOT WARRENTED	
J_{CX}	6.5	4.5	4.5

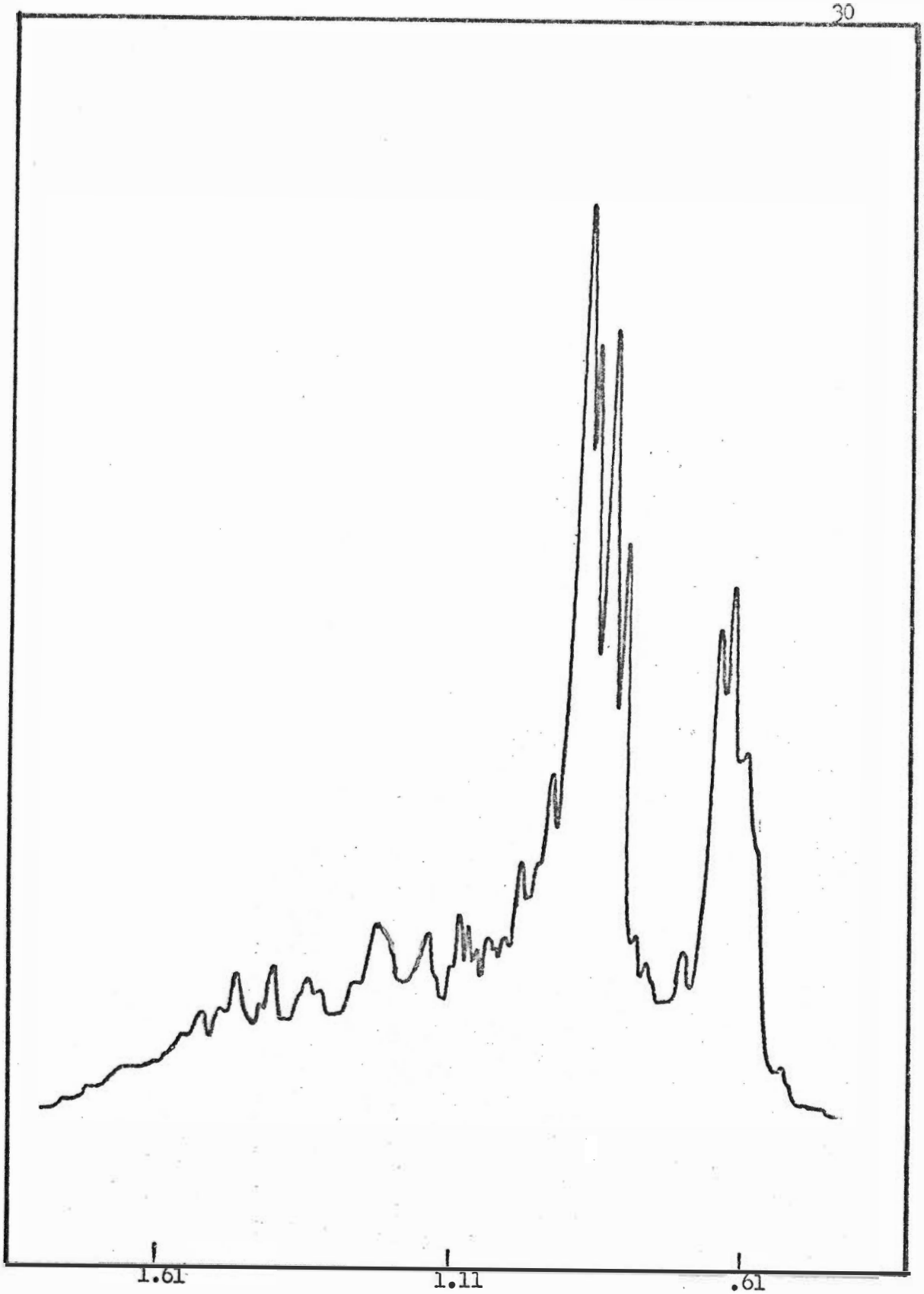
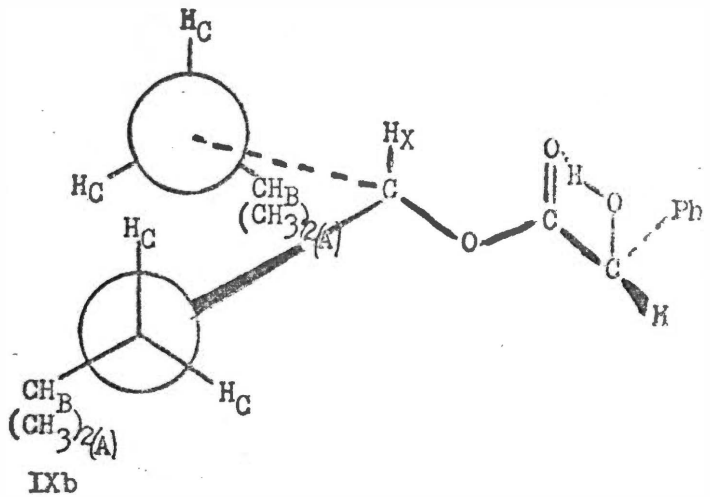


Figure 5. Methyl, methylene and isopropyl methine region of 2,6-dimethyl -4-heptyl mandelate @ 100MHz.



IXb

E. 1,3-Diphenyl-2-Propyl Mandelate

The spectrum of the alcohol 1,3-diphenyl-2-propanol is rather simple and contains in the aliphatic region a splitting pattern characteristic of an A_4X system: a doublet at 267.8 Hz for the methylene protons and a quintet at 380.3 Hz for the methine proton. The phenyl region consists of a singlet at 718.5 Hz.

The mandelate ester of this alcohol displays a very unique spectrum. The methylene region shows a doublet of doublets centered at 313 Hz and 293.8 Hz suggestive of nonequivalence of the two methylene resonances, although the protons of each geminal pair apparently have the same chemical shift. The methine proton of the ester is shifted downfield approximately 140 Hz to 520.8 Hz.

The unique characteristic of this spectrum appears in the aromatic region. Experiments to be described later indicate that

the phenyls of the alcohol moiety appear as two absorptions with the upfield phenyl showing some second order splitting. The mandelate phenyl is split into two broad multiplets with a ratio of 3:2 separated by approximately 28 Hz. These were later identified as the two ortho protons at a chemical shift of approximately 698 Hz. The meta protons appear at approximately 690 Hz and the para at approximately 670 Hz.

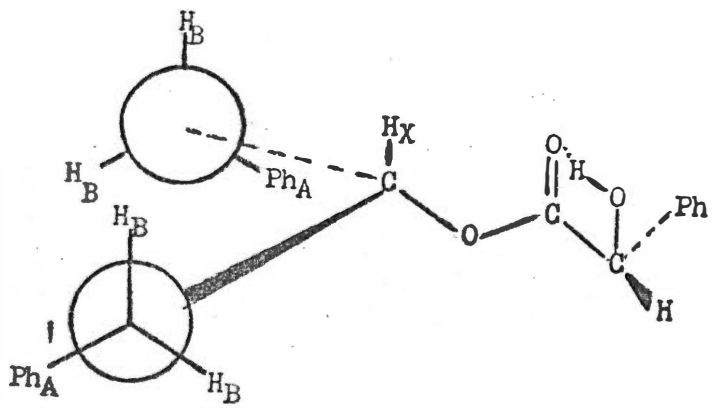
Very large chemical shifts are commonly observed in the spectra of compounds containing paramagnetic species because of the large magnetic moments of unpaired electrons by pseudo-bonding at a point of high electron density, these are called "Chemical Shift Reagents."[13] Although both carbonyl and hydroxyl oxygens may act as acceptor sites for the shift reagent it has been demonstrated that there is a strong preference to pseudo-bonding at the hydroxyl oxygen.[14]

Several samples of the mandelate were prepared with varying known concentrations of deuterated 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octane-dionato-Europium ($Eu(fod)_3$-d_{27}). The shift reagent bonding to the mandelate hydroxyl altered significantly the aromatic region of the spectra. The most significant shift occurred to the acid phenyl, which shifted downfield past the benzyl phenyls.

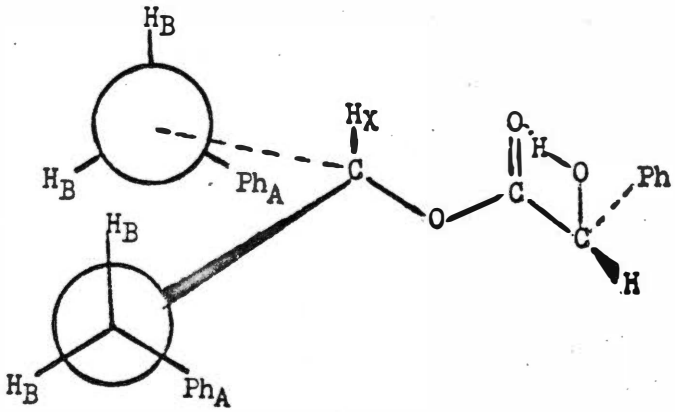
It can be assumed that because of the upfield shift of one of the benzyl phenyls along with the acid phenyl relative to the parent compounds, that these phenyls are oriented in such a way that mutual shielding is occurring. The two ortho protons in the acid

moiety lie closest to the center of the upfield benzyl ring. Further confirmation of such an orientation can be supported using calculations involving the Johnson and Bovey rules for benzene shielding.[15] Calculations using Dreiding models were employed on the two mutually shielded phenyl groups, and the results are compiled in Table 6. The phenyls lie at an angle of approximately 37° from being parrallel and calculations show the ortho protons of the mandelate are highly shielded by the benzyl phenyl cone and at the same time these two ortho protons are closer to the hydroxyl group, explaining the origin for a greater shift downfield upon addition of the shift reagent.

Structures Xa and Xb show two possible conformations of the ester. The two phenyl groups as explained previously must be lying in each others shielding region, thus leaving trans and gauche orientations for the methylene protons relative to the hydroxyl methine. Thus due to the coupling constant of 6.5 Hz we assume that the front phenyl group must rotate back and forth, otherwise if both methylenes protons were gauche then the coupling constant would be considerably smaller.



Xa



Xb

Table V and VI along with Figures 6, 7, 8, 9 and 10 show the data obtained from the NMR spectrum.

TABLE V

SPECTRAL PARAMETERS (IN HZ) FOR 1,3-DIPHENYL-2-PROPANOL AND 1,3-DIPHENYL-2-PROPYL MANDELATE AT 100 MHZ

	1,3-Diphenyl-2-Propanol	1,3-Diphenyl-2-Propyl Mandelate	
		Low-Field Benzyl Group	High-Field Benzyl Group
ν_X	380.3	520.8	
ν_A	718.5	718	711
ν_B	267.8	313.8	293.8
J_{BX}	6.5	6.5	6.5

TABLE VI

DATA ON BENZENE SHIELDING EFFECT

$\Theta = 37^{\circ}$

	Observed	Calculated
H_A	$\Delta\delta = 54$	$Z = 2.3$ [a] $\rho = 1.5$ [a] $\Delta\delta = 55.7$
H_A'	$\Delta\delta = 54$	$Z = 2.3$ $\rho = 1.5$ $\Delta\delta = 55.7$
H_B	$\Delta\delta = 31$	$Z = 3.2$ $\rho = 1.6$ $\Delta\delta = 30.9$
H_C	$\Delta\delta = 31$	$Z = 3.2$ $\rho = 1.6$ $\Delta\delta = 30.9$
H_D	$\Delta\delta = 23$	$Z = 3.8$ $\rho = 1.4$ $\Delta\delta = 24.8$

[a]Values in ring radii.

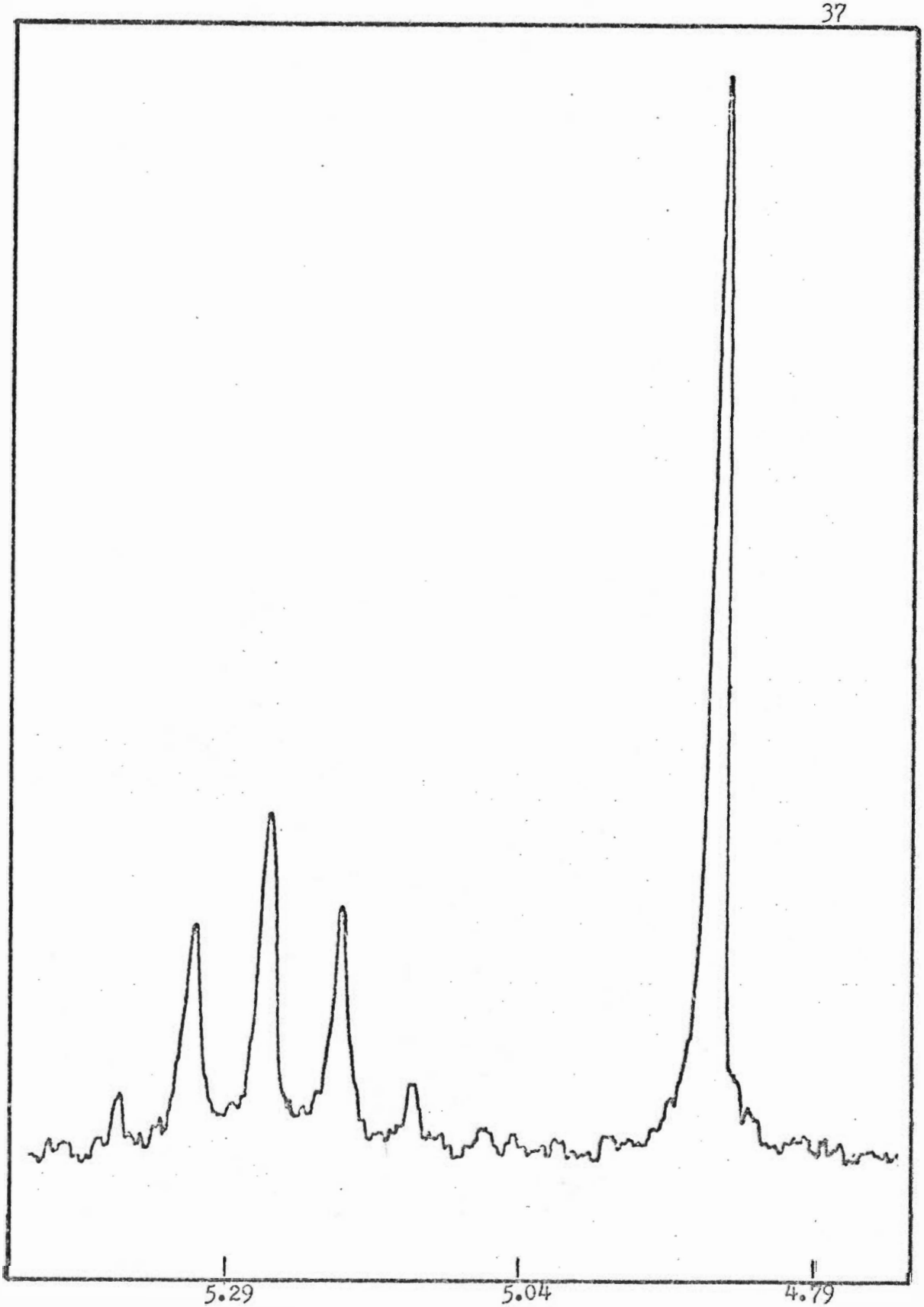


Figure 6. Methine region of 1,3-diphenyl-2-propyl mandelate @ 100MHz.

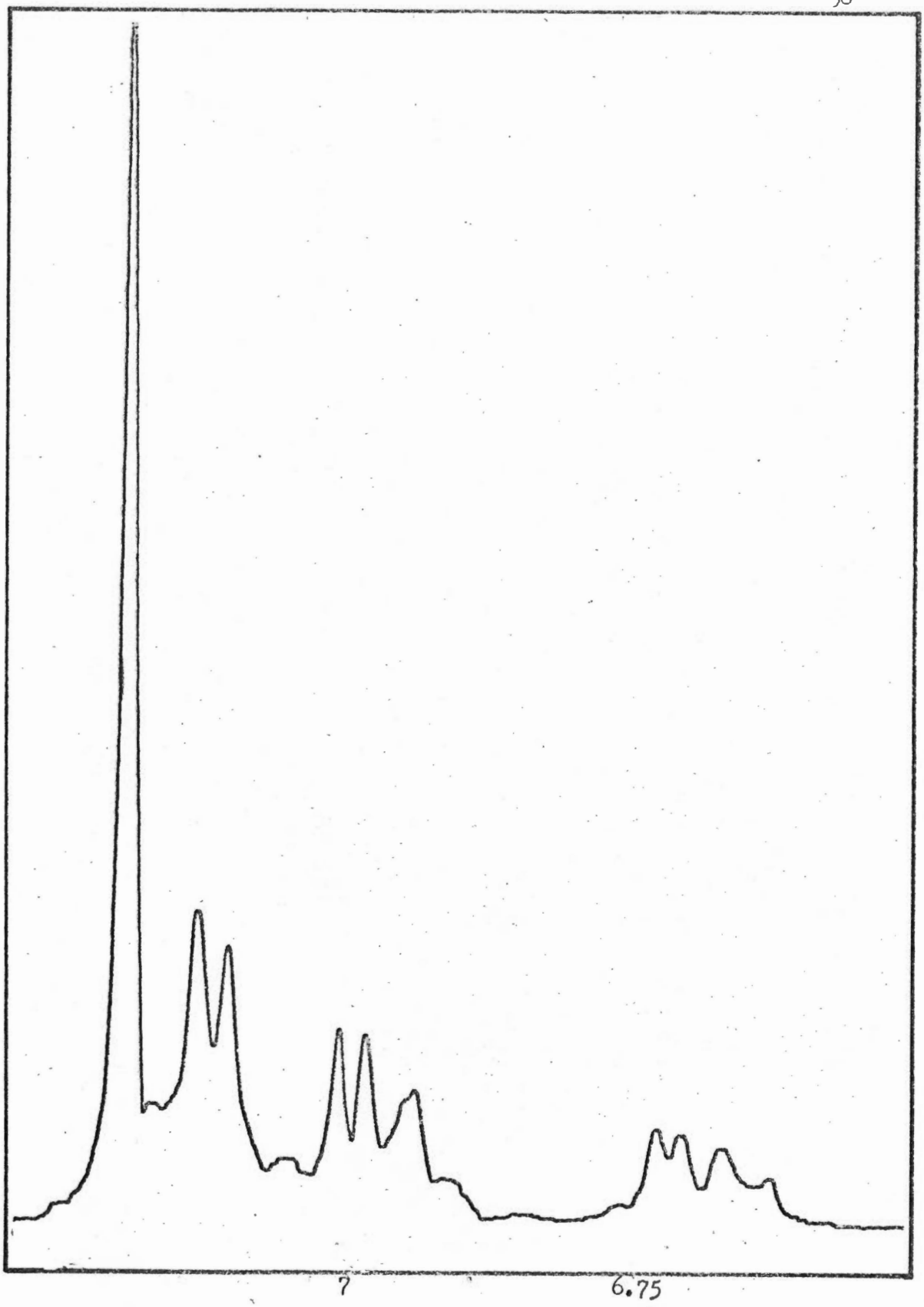


Figure 7. Aromatic region of 1,3-diphenyl-2-propyl mandelate @ 100MHz.

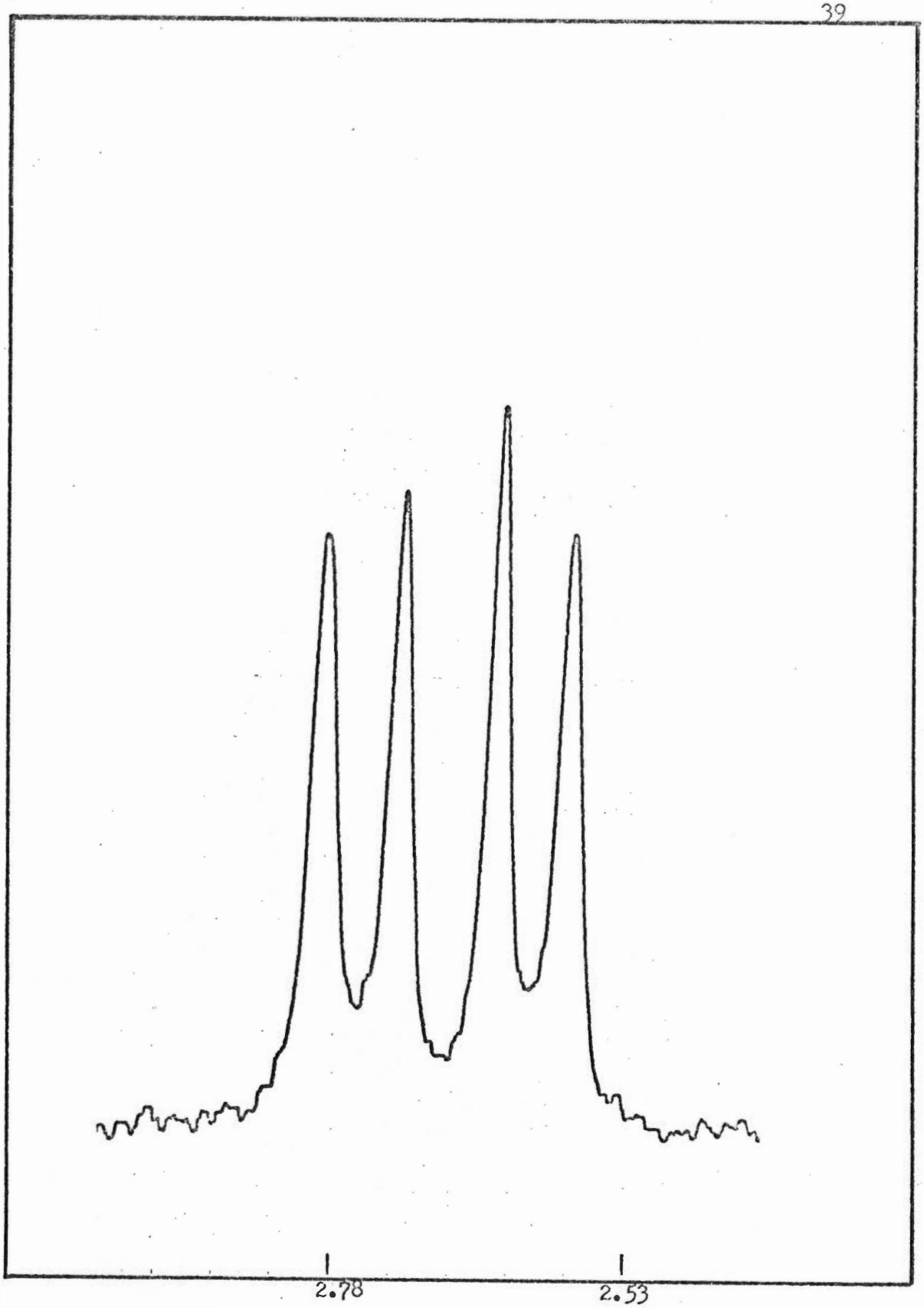


Figure 8. Methylene region of 1,3-diphenyl-2-propyl mandelate @ 100MHz.

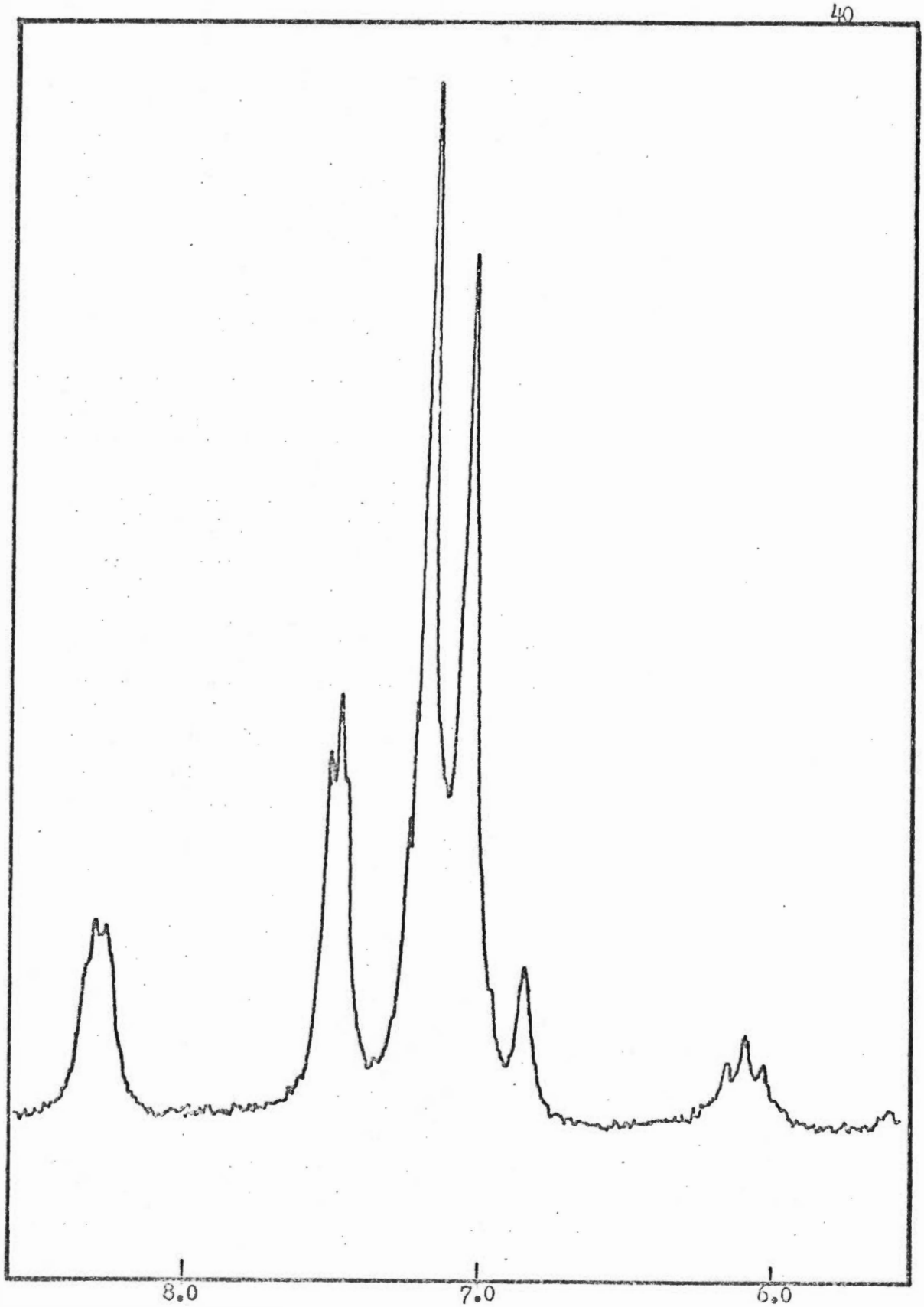


Figure 9. Aromatic region of 1,3-diphenyl-2-propyl mandelate with 10^{-4} mole of shift reagent @ 100MHz.

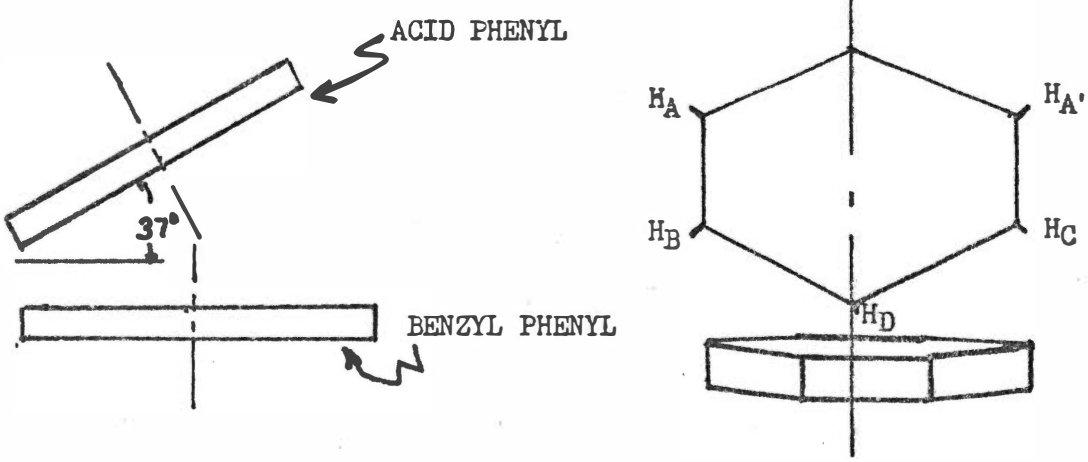


Figure 10. Conformation of the two mutually shielding phenyl groups.

CHAPTER IV

SUMMARY

The results of these studies on magnetic nonequivalence of mandelates demonstrate both the generality and the extent of nonequivalence upon proton nuclear magnetic resonance in relatively complex spin-spin systems. It is evident that the esters studied offer another example of the growing list of compounds which display magnetic nonequivalence because of the presence of a center of asymmetry rather far removed from the site of nonequivalence. It is reasonable to suppose that this is basically a result of differences in the populations of conformations rather than an effect due to intrinsic asymmetry. In the compounds investigated, nonequivalence is displayed by protons or groups not necessarily bonded directly to the asymmetric center, but is highly dependent on the nature of the substituents at the asymmetric center, notably the phenyl group. The origin of this behavior is complex in that changes in the molecule more than six atoms removed affect the magnetic nonequivalence.

There are therefore vast numbers of possible conformations, and on the data gathered, it seems impossible to make a simple correlation between the degree of magnetic nonequivalence and any single parameter. The values obtained, however, do suggest that certain structural features may be more important than others. As was noted earlier, the behavior of the esters could be explained if the groups

are oriented relative to the asymmetric center in such that the two groups on either side of the hydroxyl carbon are unequally shielded.

The only explicitly analyzed spectrum is the 3-pentyl mandelate which was calculated with a NMRIT-NMREN program. The values and information gathered here can be and were used to interpret results for the other more complex systems by analogy. These data are not incompatible with the explanation proposed for the other esters, namely the 2,4-dimethyl-3-pentyl mandelate.

Finally the origin of unequal shielding of groups such as the two upfield methyl groups in 2,4-dimethyl-3-pentyl mandelate and 2,6-dimethyl-4-heptyl mandelate can only be speculated on. Table VII summarizes the methyl shift differences in each of the systems studied as a function of chain length. The data show that nonequivalence increases through pentyl and then begins to decrease. This suggests that protons three bonds removed from the carbinol carbons are at an optimum distance to lie in the shielding cone of the phenyl ring.

TABLE VII

SOME METHYL CHEMICAL SHIFTS OF MANDELATE ESTERS OF DIALKYL CARBINOLS, R_2CHOH[a]

R=	Downfield Methyl	Upfield Methyl(s)
CH_3-		
(Isopropyl)	1.23	1.06[b]
CH_3CH_2 - (3-Pentyl)	0.84	0.48
$CH_3CH(CH_3)$- (2,4-Dimethyl-3-Pentyl)	0.87	0.53, 0.48
$CH_3CH_2CH_2$- (4-Heptyl)	0.92	0.67
CH_3CHCH_2- (CH_3) (2,6-Dimethyl-4-Heptyl)	0.89, 0.86	0.63, 0.75

[a]Isopropyl Acetate $\delta = 1.23$

[b]Values given in p.p.m.

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BIBLIOGRAPHY

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VITA

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